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EDITORIAL COMMENT

Implementation of miRNAs to Reduce In-Stent Restenosis in the Future*

Gary L. Schaer, MD,† Chunxiang Zhang, MD, PhD‡

Vascular responses to angioplasty include elastic recoil, dissection, and neointimal formation. Stent implantation is superior to balloon angioplasty alone, because it successfully prevents and/or treats vascular elastic recoil and dissection. However, bare-metal stents promote neointimal hyperplasia, the major cause of in-stent restenosis. The development of drug-eluting stents (DES) has been one of the major revolutions in the field of interventional cardiology (1). By inhibiting neointimal hyperplasia, DES dramatically reduce restenosis and target vessel revascularization compared with bare-metal stents.

However, the drugs that elute from the current generation of DES are nonselective. In addition to inhibiting smooth muscle cell proliferation and migration, which is their therapeutic effect, they also suppress endothelial cell growth and mobility, which may contribute to adverse consequences such as delayed or impaired re-endothelialization, the need for prolonged dual antiplatelet therapy, and stent thrombosis (2). Thus, despite the clinical benefits of DES in reducing restenosis, there continue to be concerns about the long-term risk of myocardial infarction and cardiac death. Reducing these risks presents a key challenge to both the clinical cardiologist and basic vascular biologist, and represents a major focus of interventional cardiology research as future generations of DES are developed.

Micro-ribonucleic acids (miRNAs), with tremendous biological functions, are a class of endogenous, small, noncoding RNAs that directly regulate more than 30% of genes in a cell. Recent studies have demonstrated that miRNAs play critical roles in vascular integrity, inflammation, and disease (3). However, direct evidence has been missing as to whether miRNAs are involved in restenosis in stented arteries and whether miRNA modulators could be used as novel eluting drugs in vascular stents.

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In this issue of the *Journal*, McDonald et al. (4) report that a decrease in miRNA-21 (miR-21) reduces in-stent restenosis and inflammation in stented arteries. Using microarray analysis, they identified for the first time that multiple miRNAs were aberrantly expressed in stented pig arteries. Among them, a group of inflammatory miRNAs, including miR-21, were increased. Strong activation of miR-21 was also detected in a human coronary artery after DES implantation. Using a mouse vascular stent model, they then found that the knockout of miR-21 attenuated neointimal formation post-stenting via modulating smooth muscle cell functions and the inflammatory response as shown by enhanced levels of anti-inflammatory M2 macrophages.

There are several important aspects of this study. First, large animal models, such as the pig stent model, are an important bridge between small animal models and human stent implantation. Although miRNA profiles in arteries after angioplasty have been well studied in small animals, such as rats and mice, to the best of our knowledge, this is the first study to show the expression signatures of miRNAs in both normal and stented pig arteries. Second, although the biological roles of miR-21 in smooth muscle cells have been well-studied

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From the †Division of Cardiology, Cardiovascular Research Center, Rush University Medical Center, Chicago, Illinois; and the ‡Department of Pharmacology, Cardiovascular Research Center, Rush University Medical Center, Chicago, Illinois. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

in balloon-injured vascular walls (5), its roles in the inflammatory response in stented arteries and in-stent stenosis have not been reported. In addition, using miRNA knockout mice to study the vascular response to stenting stands as an innovative aspect of this study. Moreover, the demonstration of miR-21 expression in a stented human coronary artery is an important translational feature of the work by McDonald et al. (4), although this result should be verified by additional human samples.

We have identified some weaknesses of the study. First, the miRNA microarray used was intended for human miRNAs. Although this human array works well for conserved human/pig miRNAs on pig samples, it performs less well for miRNAs that are not conserved. Second, miR-21 is broadly expressed in all the cells related to vascular responses after stent implantation such as endothelial cells, platelets, smooth muscle cells, and inflammatory cells. The effects of miR-21 on platelet activation and endothelial cell recovery should also be tested, in addition to its effects on smooth muscle cells and inflammatory cells. At the tissue level, re-endothelialization should be determined in addition to neointimal formation. It should be noted that, although the miRNA knockout mouse is an outstanding approach to study miRNAs after vascular stenting, we should keep in mind that knockout mice may have compensative responses. Thus, a pharmacological approach in addition to a genetic approach is optimal.

To date, miRNAs are known to be critical regulators for all the cellular events after angioplasty and stent implantation, including endothelial cell recovery, smooth muscle cell migration and proliferation, platelet activation, and leukocyte activation. Importantly, the expression and biological functions of miRNAs are cell-specific. For example, miR-145 is highly expressed in vascular smooth muscle cells, but not expressed in other vascular cells (6). Also, miR-145 has a strong effect on smooth muscle cells, but not on endothelial cells. More excitingly, miRNA could have an opposite cellular effect on different vascular cells. For example, miR-221 and miR-222 have effects of pro-proliferation, promigration, and antiapoptosis on smooth muscle cells, but have antiproliferative, antimigration, and proapoptotic effects on vascular endothelial cells (7). All the previously noted features of miRNAs suggest that miRNA modulators could be used as novel eluting drugs in vascular stents. Indeed, we have shown that inhibition of miR-221 and miR-222 could reduce vascular neointimal formation, but enhance re-endothelialization after angioplasty (7). The vascular effects of miR-221 and miR-222 modulator match very well with the requirements of novel eluting drugs in vascular stents.

miRNAs could be successfully upregulated by their pre-miRNAs or miRNA mimics both in cultured cells in vitro and in injured arteries in vivo via local delivery with transfection reagents. On the other hand, miRNA expression could be successfully downregulated by many types of miRNA inhibitors. For long-term miRNA modulation, miRNA expression could be regulated by virus vectors (adenovirus, lentivirus, or adeno-associated virus) expressing miRNAs or their inhibitors. To date, the coating method of miRNA modulators on stents and their delivery and/or release into vascular walls via stents have not been established.

Another challenge to the use of miRNA modulators as eluting drugs is the selection of a therapeutic strategy. It is well known that multiple miRNAs may participate in the vascular responses post-stenting. However, each miRNA may only have a modest effect. Thus, multiple modulators or a "therapeutic cocktail" should be selected and their interactions characterized before they are used in vascular stents. Although the biological functions of miRNAs in vascular smooth muscle cells and endothelial cells after angioplasty are well studied, more research is needed on the role of miRNAs in platelets and leukocytes after angioplasty. Obviously, more stented human vessels should be used for miRNA studies in the future. Finally, the therapeutic effects of vascular stents with miRNA modulators should be clarified in both small and large animals as a prelude to their use in clinical trials.

Although we still have a long way to go before miRNA modulators are clinically used as novel eluting drugs in vascular stents, an increasing body of evidence suggests that DES with miRNA modulators (a miR-stent) may overcome some of the pitfalls of current vascular stents. Thus, the genetic stent may represent the next generation of vascular stents.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Chunxiang Zhang, Cardiovascular Research Center and Department of Pharmacology, Rush University Medical Center, 1735 West Harrison Street, Cohn Building, Suite 406, Chicago, Illinois 60612. E-mail: chunxiang_zhang@rush.edu.

REFERENCES

1. Agostoni P, Vermeersch P. Bare-metal versus drug-eluting coronary stents. N Engl J Med 2008; 358:2516–7.

2. Chen JP. Safety and efficacy of the drug-eluting stent: a double-edged sword? South Med J 2008; 101:123–4.

3. Zhang C. MicroRNAs in vascular biology and vascular disease. J Cardiovasc Transl Res 2010;3: 235–40.

4. McDonald RA, Halliday CA, Miller AM, et al. Reducing in-stent restenosis: therapeutic manipulation of miRNA in vascular remodeling and inflammation. J Am Coll Cardiol 2015;65: 2314–27.

5. Ji R, Cheng Y, Yue J, et al. MicroRNA expression signature and antisense-mediated depletion reveal an essential role of microRNA in vascular neointimal lesion formation. Circ Res 2007;100: 1579–88.

6. Cheng Y, Liu X, Yang J, et al. MicroRNA-145, a novel smooth muscle cell phenotypic marker and modulator, controls vascular neointimal lesion formation. Circ Res 2009; 105:158–66.

7. Liu X, Cheng Y, Zhang S, et al. A necessary role of miR-222 and miR-221 in vascular smooth muscle cell proliferation and neointimal hyperplasia. Circ Res 2009;104:476–87.

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